Low carbohydrate diets represent a popular form of recrudescent food faddism. Although most revolve around the emphatic theme that carbohydrates are to blame for many chronic diseases, their specific ideologies are more variable and in some cases quite sophisticated. The Zone Diet phenomenon represents a new generation of modern low carbohydrate food fad with sales placing it among the most popular diet books in recent history. The Zone is a 40% carbohydrate, 30% protein, and 30% fat eating plan that advocates only sparing use of grains and starches. The precise 75 protein to carbohydrate ratio required with each meal is promoted to reduce the insulin to glucagon ratio, which purportedly affects eicosanoid metabolism and ultimately produces a cascade of biological events leading to a reduction in chronic disease risk, enhanced immunity, maximal physical and mental performance, increased longevity, and permanent weight loss. There is presently little scientific support for the connections made between diet, endocrinology, and eicosanoid metabolism. In fact, a review of the literature suggests that there are scientific contradictions in the Zone Diet hypothesis that cast unquestionable doubt on its potential efficacy. The purpose of this review is to evaluate the scientific merit of the Zone Diet and its health claims in an effort to help delineate what is and what is not sound nutrition science.
Review

The Zone Diet Phenomenon: A Closer Look at the Science behind the Claims

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Key words: low carbohydrate diet, 40/30/30 diet, protein-carbohydrate ratio, insulin-glucagon ratio, eicosanoids

The purported health benefits of low-carbohydrate diets have been advocated intermittently over the last century and have enjoyed increasing popularity over the last decade. Although most revolve around the emphatic theme that carbohydrates are to blame for many chronic diseases, their specific ideologies are more variable and in some cases quite sophisticated. The Zone Diet phenomenon represents a new generation of modern low carbohydrate food fad with sales placing it among the most popular diet books in recent history. The Zone is a 40% carbohydrate, 30% protein and 30% fat eating plan that advocates only sparing use of grains and starches. The precise 0.75 protein to carbohydrate ratio required with each meal is promoted to reduce the insulin to glucagon ratio, which purportedly affects eicosanoid metabolism and ultimately produces a cascade of biological events leading to a reduction in chronic disease risk, enhanced immunity, maximal physical and mental performance, increased longevity and permanent weight loss. There is presently little scientific support for the connections made between diet, endocrinology and eicosanoid metabolism. In fact, a review of the literature suggests that there are scientific contradictions in the Zone Diet hypothesis that cast unquestionable doubt on its potential efficacy. The purpose of this review is to evaluate the scientific merit of the Zone Diet and its health claims in an effort to help delineate what is and what is not sound nutrition science.

Key teaching points:

• The Zone Diet is a carbohydrate-restricted diet that postulates a connection between diet, hormones and eicosanoids that ultimately leads to improved health.

• There is no evidence that a 0.75 protein to carbohydrate ratio (40/30/30), whether eaten as a small test meal or in the form of a complete mixed diet, reduces the insulin response when compared to traditional dietary guideline meal/food intakes and may even potentially produce a larger area under the insulin curve.

• The Zone classification of eicosanoids as “bad” or “good” based on receptor binding or on gross physiological functions is oversimplified, but the recommendation to supplement the diet with omega-3 fatty acids or progenitors of series-1 eicosanoids has some documented health merit.

• Although carbohydrate, protein, insulin and glucagon can impact delta dehydrogenase enzyme activity, those activities reported by the Zone clearly and selectively ignore the known effects of macronutrients and hormones that contradict the Zone theory.

• The scientific literature is in opposition to the purported benefits of adopting a Zone Diet for improved health.

INTRODUCTION

The purported health benefits of low-carbohydrate diets have been advocated intermittently over the last century and have enjoyed increasing popularity over the last decade. Although the extremity of dietary carbohydrate restriction varies among popular low carbohydrate diets, the belief that carbohydrates are in one way or another to blame for most chronic diseases remains a consistent and emphatic theme. On the other hand, the theories offered to explain the association between lower carbohydrate intakes and improved health are more variable and have become progressively more sophisticated. For the credulous consumer identifying with the recognized link between science, nutrition and health, the appearance of a
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scientific basis for popular low carbohydrate diet claims is alluring. The Zone Diet phenomenon represents a new generation of modern low carbohydrate food fad with sales placing it among the most popular diet books in recent history.

The Zone Diet’s theoretical basis is intricate, and some of its detailed content enigmatic. As a result, many health and nutrition scientists choose simply to dismiss its health claims. However, while the Zone Diet is generally regarded as fiction, the foundations for its theories are based on real scientific facts. Since even a pure myth usually contains a particle of truth, an unbalanced dismissal of the Zone Diet argument is ineffective in combating its claims and may even serve to perpetuate confusion among the popular media when nutrition and health professionals attempt communicating to the consumer what is and what is not sound nutrition science.

Carbophobia is a form of nutrition misinformation infused into the American psyche through multiple advertising avenues that include magazine ads, television infomercials and especially best selling diet books. Due to the freedom of press guaranteed under the First Amendment, the lucrative publication of dubious nutrition information is difficult to combat. The success of the Zone Diet book by Barry Sears [1] in 1995 led to publication of at least ten Zone-related books or Zone “knock-offs”. The American Dietetic Association promotes dissemination of sound, science-based nutrition information to correct and counter pervasive nutrition misinformation [2]. Therefore, the purpose of this review is to evaluate the scientific merit of the Zone Diet and its health claims in an effort to help delineate what is and what is not sound nutrition science.

WHAT IS THE ZONE DIET?

The recommendation to achieve a dietary macronutrient distribution of approximately 55% carbohydrate, 15% protein and 30% fat is widely acknowledged and based upon an extraordinary depth of scientific research spanning more than 25 years [3–7]. In contrast, the Zone Diet is defined as a 40% carbohydrate, 30% protein and 30% fat eating plan that specifically advocates sparing use of grains and starches [1]. More importantly, the protein to carbohydrate ratio (P:C) of the diet is 0.75, or 3g of protein for every 4g of carbohydrate. This is approximately three times the ratio (0.25) resulting from conventional diet recommendations. According to Zone Diet doctrine, every meal must conform to this 0.75 P:C in order to realize the purported health benefits. The Zone Diet prescription is centered primarily on protein intake, which is specified as 1.1–2.2 g/kg fat-free mass, depending on activity level [1]. The carbohydrate component is derived from the desired 0.75 P:C, while fat intake makes up the remaining 30% of total energy. The Zone Diet prescription for three body mass indexes (BMI) and corresponding body fat percentages [8] associated with the need for weight loss are presented in Table 1. Assuming a sedentary lifestyle, Table 1 makes it clear that a Zone Diet is both a low energy and low carbohydrate diet. Once a desired amount of body fat is lost, dieters may add fat back to the diet to maintain appropriate body fat levels while keeping the P:C of the diet and every meal at 0.75. In this way, the Zone transforms from a weight loss diet to a lifestyle diet [1,9].

The “Zone” is defined as a metabolic state in which the human body operates at optimal efficiency [1]. The specific health benefits of the Zone Diet purportedly include, but are not limited to, permanent weight loss, prevention of chronic diseases, enhanced immunity, maximum physical and mental performance and even greater longevity [1]. Zone Diet claims of maximum physical performance have been both refuted [10–13] and rebutted [14]; however, all benefits attributed to the Zone Diet are based on the same mechanistic premise. Fig. 1 illustrates the proposal that a 0.75 P:C will reduce the insulin to glucagon ratio (I:G), allow excess body fat to be “burned” (weight loss) and ultimately lead to the production of “good” eicosanoids [1,9]. According to the Zone theory, eicosanoids are extremely powerful biological agents and the specific production of “good” eicosanoids is responsible for all the diet’s purported health benefits [1]. Therefore, the Zone Diet is a carbohydrate-restricted diet that postulates a connection between diet, hormones and eicosanoids that ultimately leads to improved health. The scientific questions of interest in this review are 1) Does changing the dietary P:C from 0.25 to 0.75 alter the insulin to glucagon ratio (I:G) enough to reduce or suppress the anabolic actions of insulin? 2) Can an alteration in the I:G result in the precise control of eicosanoid metabolism?

THE SCIENCE BEHIND THE ZONE: A CLOSER LOOK

Diet and Blood Glucose Homeostasis

The endocrine pancreas produces two hormones that regulate blood glucose concentrations. Insulin is a glucose-lowering

| Table 1. Sample Zone Diet Prescriptions at Three Undesirable Body Mass Indexes |
|-----------------------------|----------------|-------------|----------------|----------------|----------------|----------------|------------|
| Ht. (m) | Wt. (kg) | BMI (kg/m²) | Body Fat (%) | FFM (kg) | PRO (g)² | CHO (g) | FAT (g) | Energy (MJ) |
| 1.52 | 59.9 | 26 | 20 | 48.1 | 53 | 71 | 24 | 2.97 |
| 1.68 | 79.8 | 28 | 25 | 59.9 | 66 | 88 | 29 | 3.68 |
| 1.83 | 99.8 | 30 | 30 | 69.8 | 77 | 103 | 34 | 4.31 |

¹ Body fat associated with corresponding BMI descriptor [8].
² Assumed sedentary: 1.1 g/kg FFM [11].
The Zone Diet Phenomenon

40/30/30 Diet
(P:C = .75)

↓

Decrease in I:G

↓

Good Eicosanoid Synthesis

↓

SUPERIOR HEALTH

Fig. 1. Postulated biological sequence of events linking a lower carbohydrate intake with a state of superior health known as the Zone [19] (P:C = protein to carbohydrate ratio; I:G = insulin to glucagon ratio).

hormone produced by pancreatic beta cells while neighboring alpha cells produce its antagonist glucose-raising hormone glucagon. The exact mechanisms to explain the control of blood glucose homeostasis have been recently clarified in a series of intricate glucose, insulin and glucagon clamping studies. Fig. 2 illustrates that, within the physiological range of fasting and postprandial blood glucose concentrations, glucose homeostasis is achieved almost exclusively by variations in insulin release and withdrawal [16–18]. It is only when blood glucose concentrations fall below this biological range that glucagon and other counterregulatory hormones prevent or correct hypoglycemia in a hierarchical manner. Both glucagon activity and release are suppressed through one or more mechanisms involving direct or indirect alpha cell inhibition by glucose, glucose transport, glucose metabolism, or insulin [16,19–22].

In the most simplistic sense, the net metabolic trend toward anabolism (insulin) or catabolism (glucagon) depends on the insulin to glucagon ratio (I:G). However, the metabolic release of insulin and glucagon are so highly sensitive to blood glucose concentrations that the activity of glucagon is largely suppressed in the postprandial period so long as blood glucose concentrations remain within the physiological range [16–18] (Fig. 2). For example, ordinary postprandial insulin concentrations (25–100 μU/mL) abolish the lipolytic actions of glucagon (200 pg/mL) [23] during euglycemia both in vitro [24] and in vivo [25].

The classic insulin and glucagon responses to the ingestion of single nutrients are well documented. Carbohydrates (hyperglycemia) stimulate insulin release while protein (hyperaminoacidemia) stimulates the release of glucagon and insulin [16,26–28]. The hormonal response to protein intake promotes amino acid uptake and protein synthesis (insulin) while preventing hypoglycemia (glucagon) [16]. This is conceivably an advantageous evolutionary adaptation for any carnivorous animal subsisting largely on a meat diet. However, when protein and carbohydrate are consumed mixed together, a synergy is produced resulting in a larger release of insulin when compared to carbohydrate or protein eaten alone [29–31]. According to the principles of the Zone Diet [11], a 0.75 P:C (acceptable range of 0.6–1.0) represents the ideal macronutrient balance to reduce plasma insulin and shift the I:G ratio in favor of the catabolic, lipolytic hormonal milieu most suitable for weight loss and “good” eicosanoid production (discussed below). Because there are no peer-reviewed scientific data on the Zone Diet that would specifically allow an explicit examination of this claim, related literature must be examined and the implications of these data extrapolated to the Zone condition.

Protein/Carbohydrate Ratios and the Endocrine Pancreas

Spiller et al. [29] fed different combinations of liquid P:C food boluses to normal subjects and measured their acute (2 hour) glucose and insulin responses to those meals. The results of these experiments [29] showed that the area under the curve (AUC) for glucose was significantly greater for a P:C of 0.27 (conventional diet recommendations) than either 0.58 or 0.86 (ratios within Zone Diet recommendations). However, this difference was due solely to what occurred in the first 30-minute postprandial period, and blood glucose levels returned to normal in each condition within ~60 (0.27), ~45 (0.58) and ~35 (0.86) minutes, respectively [29]. More importantly, the AUC for insulin was not different among the three P-C’s. Therefore, the release and withdrawal of insulin required to regulate these small differences in blood glucose was similar for all three dietary ratios.

Westphal et al. [30] also examined the effects of food bolus P:C’s (mixed solid and liquid food) similar to conventional (0.20) and Zone Diet (0.60, 1.0) levels on 4 hour glucose, insulin and glucagon measurements. This study showed no differences in glucose, insulin or glucagon AUC attributable to P:C ratios [30]. There was, however, a clear trend for both insulin and glucagon concentrations to be higher in proportion to higher P:C ratios. This is not surprising given the known
metabolic effects of this macronutrient combination. No statistical comparison was made among the I:G of the diets, but the data do support a reduction in I:G when the P:C is increased. However, this is of little metabolic consequence when blood glucose concentrations are within the physiological range (fasting and postprandial), since insulin suppresses the activity of glucagon. In fact, because absolute insulin areas rose in stepwise fashion as the P:C increased [30], a higher P:C could be argued to stimulate a more anabolic condition, perhaps favorable for weight gain and “bad” eicosanoid production (discussed below).

In one of the only peer-reviewed studies to examine and compare long-term (six months) effects of Zone-like (0.78) and conventional (0.24) P:C’s on human metabolism, Linn et al. [32] showed that 1) there was no significant difference in fasting lipid oxidation when people consumed either diet, 2) glucagon suppression (release) by insulin was equally sensitive on both diets, 3) the glucose threshold for insulin release was reduced by 15% after a 0.78 P:C diet, and 4) glucose sensitivity was reduced by 26% on the 0.78 P:C diet. All of these data indicate that consuming a diet with a Zone-recommended P:C (0.6–1.0) has no greater potential to promote fat burning, weight loss or any other phenomenon related to I:G alterations (see below) when compared to a diet consistent with conventional nutritional recommendations because associated insulin levels are likely to be as high or higher in response to increasing the P:C.

More complicated, but applicable, metabolic interactions of dietary protein and carbohydrate in whole-foods diets must be carefully considered. Added fat, fiber and the type of dietary carbohydrate fed can all significantly affect the I:G ratio. Coulston et al. [33] compared the effects of consuming two whole foods diets (60% carbohydrate, 21% fat vs. 40% carbohydrate, 41% fat) for ten days each on the postprandial insulin response measured at the noon-time meal (mean of days 9 and 10). The insulin response was significantly blunted for hours following the 40% carbohydrate meal when compared to the higher carbohydrate meal. These data might wrongly be interpreted to support the validity of the Zone Diet concept when in fact neither diet was Zone-like in its P:C (60% = 0.32 vs. 40% = 0.48). Since fiber intake was similar (26–35 g) for both trials, the delayed gastric emptying afforded by the higher fat intake probably explains the lower insulin levels best. There were no differences in chronic fasting glucose or insulin levels when comparing the two diets after ten days. Clearly, the metabolic response to whole food diets is not as predictable as those measured when consuming single or dual nutrients. Similarly, other complicating factors may explain many of the putative deleterious effects attributed to “high carbohydrate” diets. For example, studies of diets that provide a large portion of carbohydrates as simple sugars often observe transiently higher insulin concentrations and unfavorable blood lipid changes [33–35] (see Frayn and Kingman [36] for review). However, these have employed “high carbohydrate” diets not representative of those outlined by conventional food intake recommendations (~55% carbohydrates from fruits, vegetables, legumes and whole grains) [3–7]. To conclude, there is no evidence that a 0.75 P:C (40/30/30), whether eaten as a small test meal or in the form of a complete mixed diet, reduces the insulin response when compared to traditional dietary guideline food intakes and may even potentially produce a larger area under the insulin curve.

With regard to body weight control, any weight loss experienced by adherents to the Zone Diet prescription (40/30/30) is easily explained by the severe energy restriction of the diet (Table 1) rather than enhanced fat metabolism resulting from manipulations in the dietary P:C. Weight loss produced by a negative energy balance is hardly a new concept. However, the Zone Diet also purports that this same P:C and presumed I:G alteration provides health benefits beyond weight loss via changes in eicosanoid metabolism. Despite a lack of scientific support for the enhancement of fat metabolism claimed by Zone Diet proponents, the Zone Diet eicosanoid theory deserves evaluation since it is a relatively new and obscure wrinkle in the low carbohydrate diet phenomenon that is generally not well understood, but is widely touted as the “key” to optimal health [1].

DIET, HORMONES, AND EICOSANOID METABOLISM

Essential Fatty Acids and Eicosanoid Metabolism

Eicosanoids are the ubiquitous hormone-like products of essential dietary fatty acid (omega-3 and omega-6) metabolism. In fact, part of the essentiality of omega-3 and omega-6 fatty acids in human nutrition is attributed to the role of each in the biosynthesis of eicosanoids [37–40]. The major dietary sources of omega-6 and omega-3 fatty acids are polyunsaturated vegetable oils. The typical occidental diet provides roughly three times the omega-6 fatty acid (linoleic acid) necessary to prevent deficiency [41,42]. This is approximately ten times higher than omega-3 fatty acid (α-linolenic acid) intakes [41–43]. Because Americans also consume more longer chain omega-6’s from animal meats, but fewer longer chain omega-3’s from fatty fish [42], competitive pressure against omega-3 fatty acid incorporation into membrane phospholipids can occur [44–46].

Arachidonic acid (AA) is formed primarily from the elongation and desaturation of linoleic acid or is obtained directly from the diet and acts as the predominant tissue precursor of eicosanoids [45,47] (Fig. 3). The action of phospholipase releases AA from phospholipids within the plasma membranes of cells. AA acts as a precursor for different eicosanoids depending on the nature of both the tissue and the stimulus involved. Fig. 3 illustrates that when the metabolic pathway involves the cyclo-oxygenase (COX) enzyme system, unstable intermediates are formed that produce prostaglandins (PG), prostacyclins
Fig. 3. Simplified schematic of eicosanoid biosynthesis from food sources of omega-6 and omega-3 fatty acids or their derived metabolic intermediate progenitors GLA, DGLA, AA, and EPA (GLA = gamma linolenic acid, DGLA = dihomo-gamma linolenic acid, AA = arachidonic acid, EPA = eicosapentaenoic acid; COX = cyclooxygenase, LIPOX = lipoxigenase; PG = prostaglandin, PGI = prostacyclin, TX = thromboxane, LT = leukotriene, OH-DGLA = 15-hydroxydihomo-gamma linolenic acid; Δ5, Δ6 = delta 5 and 6 desaturase enzymes). Subscripts denote the total number of double bonds in each molecules structure and the series to which it belongs.

(PGI) or thromboxanes (TX), depending on the action of additional tissue-specific enzymes. When the pathway involves the lipoxigenase enzyme, leukotrienes (LT) are formed. Therefore, the physiological actions of eicosanoids in vivo depend largely on the tissue(s) in which they are synthesized.

The major physiological actions of the series-2/4 eicosanoids (e.g., PGE\textsubscript{2}, PGI\textsubscript{2}, TXA\textsubscript{2}, LTB\textsubscript{4}) presented in Table 2. Similar functions are observed for series-1 and series-3/5 eicosanoids arising from homologue AA precursors (Fig. 3), but with notable caveats. For example, the conversion of α-linolenic acid or omega-3 metabolite into series-3/5 eicosanoids is less efficient than for the omega-6's and their actions in vivo are also noticeably weaker [48]. However, the consumption of dietary omega-3 fatty acids or their homologue AA precursor eicosapentaenoic acid (EPA) impacts series-2/4 eicosanoid metabolism by competing for receptor sites, enzyme activity and also by competing for acylation into membrane phospholipids [43,45,49–51], thus diminishing omega-6 eicosanoid formation and function. Other series-1 and series-3 metabolites, such as 15-hydroxydihomo gamma linolenic acid (OH-DGLA) and docosahexaenoic acid (DHA) also directly inhibit rate-limiting enzymes involved in series-2/4 leukotriene [52] and prostaglandin [53] formation, respectively. These metabolic interactions play important roles in human physiology, health and disease.

**Eicosanoids in Health and Disease**

The possibility that excessive omega-6 intake and subsequent series-2/4 eicosanoid synthesis may influence untoward physiological outcomes and increase the risk for a variety of chronic diseases is receiving more attention [40,43,45,46,54]. Lands et al. [44,45] describe an algorithm that accurately predicts dietary intake of essential fatty acids and eicosanoid precursors from their plasma levels measured in triacylglycerols and phospholipids (reciprocal prediction also valid). The omega-6 to omega-3 fatty acid ratio from these measures may actually be useful as a biomarker in predicting morbidity and mortality related to cellular events linking a compromised vascular system to excessive omega-6, series-2/4 eicosanoid synthesis [45,46]. Because essential fatty acids serve as substrates for eicosanoid production, alterations in the balance of omega-3 and omega-6 fatty acid membrane phospholipid pools can influence eicosanoid synthesis and, thus, the specific physiological processes in which they are involved [39,43,45].

Most eicosanoids produce local (autocrine/paracrine) intracellular effects by binding to plasma membrane receptors to activate or inhibit second messenger systems (cAMP, cGMP or IP3/DAG) [55]. The membrane receptors for the most common second messenger system (cAMP) are coupled to adenylyl cyclase through separate stimulatory or inhibitory G-proteins. Therefore, whether an eicosanoid stimulates or inhibits cAMP formation depends on whether the eicosanoid binds to an inhibitory or stimulatory receptor [55,56]. In this way, eicosanoids are hormone-like in their temporal activation of intracellular second messengers and bi-directional mediation (stimulation or inhibition) of cellular activity.

According to the Zone theory, "bad" eicosanoids (series-2/4, Table 2) are those operating through the IP3/DAG second messenger pathway, while "good" eicosanoids (PGE\textsubscript{2}) operate through cAMP [14]. This classification is probably based on the observation that ischemic and thrombotic cardiovascular diseases are aggravated by pathologic arteriolar vasoconstriction and platelet aggregation [45,49,51]. Increasing cellular cAMP inhibits a myriad of Ca\textsuperscript{2+} dependent signal transduction pathways involved in the manufacture of platelets and platelet aggregation [37,58], while IP3/DAG second messengers promote Ca\textsuperscript{2+} release in the cell cytoplasm [51,55], thereby stimulating those pathways for platelet formation and aggregation. However, the designation of IP3/DAG as the pathway by which
“bad” eicosanoids act ignores the fact that activation of this same second messenger system is critical in the mechanism to vasodilate the cerebral microvasculature [59], an action that reduces the potential for thrombotic cerebrovascular accident.

Some eicosanoids also bind to multiple receptors, thereby stimulating more than one second messenger system. The Zone theory suggests that EP2 receptors for PGE2 are “good” because they stimulate cAMP formation, while EP3 receptors are “bad” because they inhibit cAMP formation [14]. This explanation is correct, but critically incomplete. There are also at least three other EP3 isoforms which have no effect on cAMP because they operate through different second messenger systems [60]. In addition, although EP3 knock-out mice demonstrate a reduced risk for thromboembolism [61], the absence of the EP3 receptor also produces derangements in febrile responses to pyrogens and on the regulation of bicarbonate secretion in response to duodenal acidification [62]. Clearly, an overgeneralized classification of eicosanoids as “good” or “bad” ignores the balanced effects produced by diverse actions of eicosanoids in human physiological regulation [63].

The Zone Diet recommendation to supplement with omega-3 fatty acids (specifically EPA or fish oil) and progenitor series-1 eicosanoid homologues of AA (GLA/DGLA) is not novel but is consistent with conventional diet and health recommendations. The modest intake of fish, fish oil, EPA supplements or plant omega-3 fatty acids is generally associated with a reduced risk for morbidity and mortality from various chronic vascular and inflammatory diseases [40,42,49,51,64,65–67]. The mechanism to explain this health benefit has generally centered on EPA competition with AA for phospholipid membrane acylation, rate-limiting enzyme activity and receptor sites [43,45,49–51]. Although the use of omega-3 fatty acids to diminish omega-6 eicosanoid signaling is well documented, the direct impact of omega-6 eicosanoid progenitors (GLA, DGLA) on series-1 eicosanoid synthesis (Fig. 3) and reduced series-2/4 eicosanoid signaling is more equivocal.

The importance of GLA or DGLA supplementation in human nutrition has recently been reviewed as particularly promising in relieving inflammatory and rheumatic conditions [52,53,66–68]. However, human GLA and DGLA supplementation studies illustrate greater unpredictability associated with eicosanoid production and platelet aggregation. Dietary supplementation with GLA or DGLA in humans given 1–6 g doses for three to four weeks results in a rise in serum DGLA and AA concentrations [69–71]. Although 21 days of GLA supplementation decreased inflammatory LTB4 formation by 58% in one study [71], a similar dose given over 42 days increased platelet aggregation in another [72]. These conflicting results may reflect the potential for the DGLA metabolite OH-DGLA to either inhibit lipooxygenase activity directly [52] or, alternatively, undergo metabolism to AA and TXA2 (Fig. 3), thus stimulating vasoconstriction and platelet aggregation. Stone et al. [69] observed an increase in the production of both PGE1 and PGE2 after 28 days of DGLA supplementation [69]. Therefore, supplemental GLA undergoes elongation to DGLA, which undergoes ample desaturation (Δ5) to AA in vivo [70,73], despite a reportedly low Δ5 desaturase activity in man [69,73].

The Zone classification of eicosanoids as “bad” or “good” based on receptor binding or on gross physiological functions is oversimplified, but the recommendation to supplement the diet with omega-3 fatty acids or progenitors of series-1 eicosanoids has some documented health merit. Although much of how to control or manipulate omega-6 fatty acid metabolism is still unknown, according to the Zone Diet theory, dietary and hormonal control of desaturase enzyme activity can regulate eicosanoid production and metabolism with drug-like precision [1].

**Dietary and Hormonal Control of Desaturase Activity**

Dietary and hormonal effects on essential fatty acid desaturase enzyme activity have been studied for decades [73,74–83], but heretofore, no connection between diet, endocrinology, eicosanoids and health [1,15] is documented. Diet-induced reductions in the Δ9 are promoted by Zone Diet advocates as the key to controlling eicosanoid metabolism through manipulation of desaturase enzyme activity [1,15]. However, as explained above, any alteration in the Δ9 is likely to be very small and of no foreseeable metabolic consequence due to the synergistic release of insulin resulting from carbohydrate and protein eaten together and the dominant physiological actions of insulin over glucagon. Nevertheless, to be complete this analysis of the Zone theory must be considered for its proposed effects on desaturase enzyme activity because Zone advocates misleadingly offer only select scientific information in support of this health promoting metabolic pathway.

According to the Zone [1,15], carbohydrates inhibit the Δ6 desaturase enzyme (Δ6), while insulin accelerates its Δ5 desaturase counterpart (Δ5). In contrast, protein intake is said to stimulate Δ6, while the accompanying glucagon stimulus is purported to inhibit Δ5. Therefore, a smaller insulin and larger glucagon release accompanying a low carbohydrate, high protein diet would result in greater omega-6 desaturation to GLA (more active Δ6 enzyme) and less DGLA desaturation to AA (less active Δ5 enzyme), thus producing more series-1 and less series-2/4 eicosanoids (Fig. 3). However, this explanation ignores scientific findings to the contrary.

In _vitro_ animal studies clearly demonstrate that carbohydrate diets ranging from 50% to 73% of energy intake inhibit both Δ5 and Δ6 desaturase enzyme activity [74,77], an effect mediated by elevated blood glucose concentrations [83], but desaturase enzyme inhibition by glucose is rapidly reversed _in vivo_ following insulin injection [73,83]. Dietary protein intakes ranging from 20% to 73% of energy intake stimulate both Δ5 and Δ6 enzymes [74,77,78,82], while glucagon inhibits both enzymes [79,80]. These observations concerning the effects of
diet and hormones on desaturase activity is summarized in Fig. 4. It is difficult to reconcile why the Zone Diet views carbohydrate unfavorably because it inhibits Δ6, while glucagon is viewed favorably even though it too inhibits Δ6. Similarly, the Zone Diet views insulin as unfavorable because it stimulates Δ5, but protein is viewed as favorable even though it too has the same effect (Fig. 4). Although carbohydrate, protein, insulin and glucagon can impact delta desaturase enzyme activity, it is clear that information is selectively reported by Zone Diet advocates and contradictory facts are ignored (Fig. 4). In reality, the effects of glucose and amino acids on the desaturase enzymes is most notable in vitro and is likely masked in vivo by the pancreatic hormones they stimulate [81]. However, the precise regulation of desaturase enzyme function using dietary endocrinology in free-living people has never been demonstrated.

It is additionally important to recognize that desaturase enzyme activity is influenced by a multitude of other physiological and dietary variables including temperature, circadian oscillations, product feedback inhibition of other hormones operating through the cAMP second messenger and alcohol consumption [45,75,81,82,84]. In fact, the conversion of DGLA to AA may also be influenced by other factors not directly related to desaturase activity, such as competitive deacylation-reacylation reactions [85]. Pharmaceutical interventions targeted at occupying omega-6 eicosanoid receptor sites or decreasing the rate of omega-6, series-2/4 eicosanoid synthesis (e.g., aspirin), coupled with dietary changes that increase omega-3 fatty acid intakes and/or reduce omega-6 fatty acid intakes represent the only scientifically sound approach to ameliorating many of the chronic health disorders linked to excessive omega-6, series-2/4 eicosanoid signaling [45,65,86].

CONCLUSIONS

The biological plausibility of any diet and health relationship is crucial when deciding whether or not it is worthy of assessment [4]. The connection made between diet, endocrinology, eicosanoid metabolism and health [1,15] is enticing and indeed plausible. While there are no cross-sectional or longitudinal studies examining the potential health merit of adopting a Zone Diet per se, closely related peer-reviewed findings from scientific research cast strong doubt over the purported benefits of this diet. When properly evaluated, the theories and arguments of popular low-carbohydrate diet books like the Zone rely on poorly controlled, non-peer-reviewed studies, anecdotes and non-science rhetoric. This review illustrates the complexity of nutrition misinformation perpetrated by some popular press diet books. A closer look at the science behind the claims made for the Zone Diet reveals nothing more than a modern twist on an antique food fad.

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